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| 10/790,448 | 02/27/2004 | Hiroshi Kido | 02-0187 | 9915 |

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| EXAMINER | |
|---|---|
| HAGOPIAN, CASEY SHEA | |
| ART UNIT | PAPER NUMBER |
| 1615 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/790,448 | KIDO, HIROSHI | |
| | Examiner | Art Unit | |
| | Casey S. Hagopian | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Receipt is acknowledged of applicant's Request for Continued Examination/Remarks and IDS filed 10/16/2008.

No claim amendments were submitted. Claim 14 is currently pending.

### WITHDRAWN REJECTIONS

After further consideration, the examiner is withdrawing the previously submitted enablement rejection under 35 USC 112 and submitting new rejections under 35 USC 102 and 112 (scope of enablement).

### NEW REJECTIONS

After further consideration, the following rejections have been newly added:

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting proliferation of the influenza virus (page 26, lines 9-10 of Specification), does not reasonably provide enablement for preventing an influenza virus infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. To be enabling, the specification of the

patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method of preventing influenza. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the predictable nature of the art. As illustrative of the state of the art, the examiner cites Yang et al., Harper et al., and Mitra et al.

Yang et al. teaches that ambroxol suppresses influenza-virus proliferation in a mouse by increasing antiviral factor levels (abstract).

Harper et al. teaches vaccinations are the most effective means for reducing the effect of influenza (page 7). Harper et al. also teaches that the effectiveness of the inactivated influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation (page 10). Additionally, Harper discloses percentages for different

patient populations as to how effective the inactive and active forms the vaccine perform (pages 10-13).

Mitra et al. teaches compositions and methods for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms by administering a safe and effective amount of a composition comprising an amino acid salts of propionic acid nonsteroidal anti-inflammatory agent along with at least one of (a) a decongestant, (b) an expectorant, (c) an antihistamine and (d) an antitussive (see Abstract and claim 1). Mitra also names the specific expectorants, "bromhexine and ambroxol, mixtures thereof or pharmaceutically acceptable salts thereof' (see claim 3).

That references plainly demonstrate that preventing influenza is an art recognized hurdle. The references also demonstrate that influenza can be treated, proliferation can be suppressed, and the incidence thereof can be reduced, however there is nothing in the art that supports prevention of infection of the flu virus.

2. The breadth of the claims

The claim recites a method for prevention of an influenza virus infection in a warm-blooded animal comprising administering to said animal a therapeutically effective amount of a composition comprising an agent selected from ambroxol, bromhexine, pharmaceutically acceptable salts thereof and combinations thereof, and an additive. Infection is defined in the art as the process by which a viral particle (i.e., a virion) enters (i.e., injects) a host cell. See Figures 6-15 and 6-16 at pages 195 and 196 of

*Molecular Cell Biology*. Prevention as claimed in its broadest most reasonable interpretation means a virion never injects into a single host cell.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimes (dosages, timing, administration routes, etc.) necessary to prevent an influenza virus infection in all warm-blooded animals. The working examples are limited to treating and inhibiting proliferation of the influenza virus. Thus, the applicant at best has provided specific direction or guidance only for treating and inhibiting proliferation of an influenza virus infection. No reasonably specific guidance is provided concerning useful preventive protocols for an influenza virus infection.

4. The quantity of experimentation necessary

Because of the known art-recognized hurdle (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed method could be predictably used to prevent an influenza virus infection as inferred in the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the scope of enablement requirement of 35 U.S.C. 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

***Response to Arguments***

Applicant's arguments filed 10/16/2008 have been fully considered. The relevant arguments in light of the new scope of enablement rejection are discussed below. Applicant argues that the references cited by the examiner, Yang, Harper and Mitra do not explicitly state that ambroxol cannot be used to prevent infection of the flu virus. See page 4 of Remarks. Applicant further refers to Olevieri and explains that Olevieri teaches administration of ambroxol is more effective than a placebo in preventing chronic bronchitis. See pages 4-5 of Remarks. Applicant also notes that the specification states that enhanced production of pulmonary surfactants are useful for preventing any invasion of viruses into cells such as those causing chronic bronchitis. See page 5 of Remarks.

In response, it is respectfully submitted that the examiner agrees that Yang, Harper and Mitra do not expressly state that ambroxol cannot be used to prevent infection of the flu virus. However, they do not expressly state that they can be used to prevent infection of the flu virus either. The reference that applicant cites, Olevieri teaches administration of ambroxol prevents chronic bronchitis exacerbations (title). Olevieri specifically states that the treatment group had no exacerbations, lost significantly fewer days through illness and had fewer days of antibiotic therapy (abstract). Thus, the teachings of Olivieri do not support applicant's assertion that administration of ambroxol prevents infection of a cell. In fact, Olivieri further supports the examiner's position that ambroxol provides treatment/mitigation/reduction of

symptoms. Regarding applicant's statement that enhanced production of pulmonary surfactants are useful for preventing any invasion of viruses into cells such as those causing chronic bronchitis, the specification makes said statement in regards to Benne et al. The Benne reference is not listed on an information disclosure statement and thus has not been considered. Applicant is reminded that a listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. The specification does explain that the mucosal immune systems serves as a principal immunological defensive system for preventing any invasion of viruses into cells (page 2, lines 23-24). This is statement is taken to be understood by those skilled in the art that generally the purpose of the mucosal immune system is to prevent invasion of viruses into cells, however it is also understood that the mucosal immune system cannot always prevent invasion of viruses into cells. If this were in fact true, then we would be immune to viral infections and certainly that is not the case. It should be noted that the art recognizes viral infection to mean the process by which a viral particle (i.e., a virion) enters (i.e., injects) a host cell. See Figures 6-15 and 6-16 at pages 195 and 196 of *Molecular Cell Biology*. Prevention as claimed in its broadest most reasonable interpretation means a virion never injects into a single host cell. While the examiner concedes that Yang, Harper and Mitra do not explain prevention is

not possible, it is recognized by those skilled in the art that total prevention of a virion injection into a cell is not possible.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Mitra (WO 95/07103 A1).

Mitra teaches compositions and methods for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms in a mammal by administering a safe and effective amount of a composition comprising an amino acid salts of propionic acid nonsteroidal anti-inflammatory agent (i.e., an additive) along with at least one of (a) a decongestant, (b) an expectorant, (c) an antihistamine and (d) an antitussive (see Abstract and claims 1 and 8). Mitra also names the specific expectorants, "bromhexine and ambroxol, mixtures thereof or pharmaceutically acceptable salts thereof' (see claim 3). Mitra does not explicitly state the particular limitation "for preventing an influenza virus infection" found in instant method claim 14, however Mitra teaches treating, management or mitigation of flu symptoms in a mammal comprising the same ingredients. It is found that "prevention of an influenza virus" is inherent to Mitra's "treatment, management or mitigation of cold, cold-like

and/or flu symptoms" because the method of Mitra and the claimed method include the same methods steps and are treating the same patient population. Thus, Mitra implicitly teaches the claimed method.

## *Conclusion*

All claims have been rejected; no claims are allowed.

## *Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Casey Hagopian whose telephone number is 571-272-6097. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Casey S Hagopian/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615